

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 17104-006W01	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2004/043682	International filing date (<i>day/month/year</i>) 23 December 2004 (23.12.2004)	Priority date (<i>day/month/year</i>) 23 December 2003 (23.12.2003)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant NOVARTIS AG			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

<input checked="" type="checkbox"/>	Box No. I	Basis of the report
<input type="checkbox"/>	Box No. II	Priority
<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input checked="" type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

	Date of issuance of this report 26 June 2006 (26.06.2006)
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PATENT COOPERATION TREATY

REC'D	22 JUL 2005
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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2004/043682

International filing date (day/month/year)
23.12.2004

Priority date (day/month/year)
23.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, A61K31/437, A61P29/00, C07D473/00

Applicant
TRIAD THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/043682

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 in written format
 in computer readable form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/043682

Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,
 claims Nos. 55-94, 104 (industrial applicability)

because:

the said international application, or the said claims Nos. 55-94, 104 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos. 1-22 (part)
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	<input type="checkbox"/> has not been furnished <input type="checkbox"/> does not comply with the standard
the computer readable form	<input type="checkbox"/> has not been furnished <input type="checkbox"/> does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
 See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/043682

Box No. IV Lack of unity of invention

1. In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
 - paid additional fees.
 - paid additional fees under protest.
 - not paid additional fees.
2. This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
 - complied with
 - not complied with for the following reasons:

see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
 - all parts.
 - the parts relating to claims Nos.

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-104
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-104
Industrial applicability (IA)	Yes:	Claims	1-54,95-103
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Claims 55-94 and 104 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Present claim 1 relates to a group of compounds defined in such a general way that a meaningful search over the whole of the claimed scope seemed not feasible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed in the light of the description, namely those parts relating to the compounds with A = bicyclic ring, wherein each ring contains at least 2 N atoms (according to claim 23).

Re Item IV

The common structural feature of the compounds according to claim 1 of the present application is represented by the phenyl group with a specific substitution pattern, all other definitions in formula (I) are variables or comprise different possibilities (like the definition of X₁, X₂, A and D). This phenyl group with a specific substitution pattern is, however, known from the document D1 (WO 03/099820 A, cf. the generic definitions in claim 1 and the examples), which is considered as the closest state of the art for the present application. The compounds of D1 possess the same qualitative activity as those of the application (cf. page 1, line 9-13). The compounds of the present application are new vis-a-vis the compounds of D1 because of the NR₂ group of the compounds of D1. only; the definition of X₁ comprises several possibilities, but not NH or N(alkyl).

A single general inventive concept (Rule 13(1) PCT) between the different definitions of X₁ is, however, not detectable. This single inventive concept is defined as "involving one or more of the same or corresponding special technical features" (Rule 13(2) PCT), which serve to distinguish the current application from the prior art (establishes novelty) and are responsible for the inventive activity.

At least the following inventions must be considered as non-unitary (Rule 13(1) and (3)

PCT):

1. subject-matter relating to compounds with X1 = single bond
2. subject-matter relating to compounds with X1 = alkylene, C(O), CO(O), C(O)NH
3. subject-matter relating to compounds with X1 = O, S, SO, SO2

Re Item V

1. PRIOR ART

Reference is made to the following documents:

D1: WO 03/097062 A
D2: WO 03/099820 A

2. NOVELTY

The subject-matter of the claims is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1 resides in the X1 moiety. The essential structural difference between the claimed compounds and those of D2 resides in the substitution of the phenyl group.

3. INVENTIVE STEP

The subject-matter of the claims does not fulfil the requirements of Article 33(3) PCT. The closest state of the art for the present application is represented by D1. D1 discloses structurally similar heterocyclic compounds having p38 inhibiting activity which do not fall under the present application because of the difference in the X1 group, only. In the present application, such a structural variation is alleged to lead to alternative derivatives with the same qualitative activity as those described in D1. The problem underlying the present application can, however, not be seen in the provision of further novel derivatives, because the proposed solution would be seen as obvious. In view of the extremely close

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/043682

structural relationship to the compounds of D1 it is considered that the man skilled in the art would regard the new compounds of this application as being obvious alternatives to the known compounds. Furthermore, D2 discloses related compounds with the same qualitative activity and with a direct bond in the position of X1. A man skilled in the art, aware of the disclosure of D1 and D2, would have obviously expected the same qualitative properties shown by the compounds of D1 also for the present compounds. Therefore, the problem underlying the present application should be seen in the provision of new derivatives having unexpected properties over those of the closest prior art compounds (D1). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not.

Furthermore, the description appears to be completely silent about the actual testing of exemplified compounds. The breadth of the application should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based. If it turns out that the compounds of the examples of the application solve this problem it is apparent that they all have the following characteristics:

A = purin or pyrazolo[3,4-d]pyrimidin

Y-R3 = C(O)NH-cyclopropyl

R1 = Me

If those definitions are essential to the specific activity profile on which the acknowledgement of an inventive step is based, claim 1 should be restricted accordingly. In the absence of any test results it cannot be decided if the scope of the present claims represent a "reasonable generalisation" of those compounds for which it can be assumed that all the comprised possibilities actually solve the problem underlying the invention. Therefore, the subject-matter of the claims cannot be considered as involving an inventive step (Article 33(3) PCT).

Re Item VIII

An attempt is made to define additional compounds by reference to a result to be achieved. The present claims relate i.a. to compounds defined by reference to a desirable property, namely that they are "derivatives". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/043682

Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Furthermore, the term "derivative" used in the claims is vague and indefinite and as such renders the scope of the claims unclear, because the term encompasses so many possibilities that the limits of the definition are not clearly defined and thus puts undue burden on others seeking to establish the extent of the protection.

The term "pseudohalo" (i.a. in claim 1, R1) is unclear and does not fulfill the requirements of Article 6 PCT.

The term "lower" as in "lower alkyl" (i.a. in claim 1, R4, R5) is unclear and does not fulfill the requirements of Article 6 PCT.

The formula in claims 36 and 43 show compounds which appear not to be encompassed in claim 1, because the ringsystem A is substituted by 2 R13 and a carbonyl group. This leads to unclarity about the scope of claim 1 (Article 6 EPC).

A reference to the Examples should be avoided in the claims (claim 50).

Compound 1D12 on page 56 is not in the scope of the claims.